Review Article

The role of neurokinin-1 (substance P) antagonists in the prevention of postoperative nausea and vomiting

Dionne Okafor[1], Alan David Kaye[2,3], Rachel J Kaye[4], Richard D Urman[1]

[1]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, Departments of [2]Anesthesiology and [3]Pharmacology, Louisiana State University Health Science Center, New Orleans, LA 70112, [4]Department of Biochemistry, Bowdoin College, Brunswick, ME 04011, USA

Abstract

Postoperative nausea and vomiting (PONV) can be very debilitating for surgical patients, and effective management reduces potential morbidity, aiding in patient satisfaction, and minimizing the need for unintended hospital stays. Risk factors include female sex, nonsmoker, and having a previous history of motion sickness or PONV. Anesthetic risk factors include receiving opioids, not receiving a total intravenous anesthetic (TIVA), exposure to nitrous oxide, and extended length of anesthetic. Many treatments, including serotonin antagonists, dopamine antagonists, corticosteroids, inhaled isopropyl alcohol, and anticholinergics, as well as techniques such as TIVA, have been utilized over recent decades in an attempt to reduce PONV incidence. However, it remains a problem for a significant number of surgical patients. Aprepitant is a neurokinin-1 (substance P) antagonist, which exerts its effects via a final common pathway of the emetic centers after crossing the blood brain barrier. Aprepitant is commonly used in the cancer population to help prevent cancer chemotherapy-induced nausea and vomiting and has shown great promise in both acute and delayed phase PONV. Published data has shown improved efficacy when compared with ondansetron administered prior to surgery. The use of aprepitant in combination with other antiemetics potentially may help decrease unplanned hospital admissions and potentially, reduce costs associated with PONV.

Key words: Antiemetics, aprepitant, neurokinin-1 (substance P) antagonist, postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common morbidities associated with anesthesiology. The incidence is about 30% on the 1st postoperative day.[1] Nausea occurs at an incidence of about 40-50% and vomiting 25-30% depending on surgical population studied.[2] Risk factors associated with PONV can be divided into patient factors, surgical factors, and anesthetic factors. Anesthetic causes of PONV in the post anesthesia care unit (PACU) are most commonly due to the use of postoperative opioids, nitrous oxide (N_2O), and volatile anesthetics. From the surgical standpoint, laparoscopic, gynecological surgery, and cholecystectomy are high risk and found to independently increase the risk for PONV.[3]

Patient-related risk factors include female sex, nonsmokers, and having a previous history of motion sickness or PONV. Anesthetic risk factors include receiving opioids, not receiving a total intravenous anesthetic (TIVA), exposure to N_2O, and extended length of anesthetic. Nausea and vomiting can be very debilitating for some and when combined with pain from their procedure can make for a miserable experience for our patients. PONV is not only uncomfortable for patients but costly and affects patient satisfaction.[4] Unexpected

Address for correspondence: Dr. Richard D Urman, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA. E-mail: rurman@partners.org

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hospital admissions due to PONV have decreased but are still estimated to occur approximately 0.5-2% of the time.[5,6] It is, therefore, prudent that as anesthesiologists we identify those at an elevated risk and provide appropriate prophylaxis to all patients.

There are several antiemetic medications, agents, and techniques in use currently. Many treatments, including serotonin antagonists, dopamine antagonists, corticosteroids, inhaled isopropyl alcohol, and anticholinergics, as well as techniques such as TIVA have been utilized successfully over recent decades in an attempt to reduce PONV incidence. These therapies work mainly by interfering with neurotransmitter receptor signaling in the central nervous system (CNS) and gastrointestinal (GI) tract; however, none are universally effective.[2] More options are becoming available. One such option is a relatively new agent aprepitant, which has been used on cancer patients receiving chemotherapy and has shown great effectiveness for PONV.

Aprepitant and chemotherapy-induced nausea and vomiting

As in the postoperative phase, nausea and vomiting is a major complication after chemotherapy. It is regarded as the most important complication by cancer patients.[7-9] Chemotherapy-induced nausea and vomiting (CINV), reduces food intake, resulting in malnutrition, weight loss, reduced performance status which increases the incidence of hematoxicity.[10] Without prevention, acute vomiting occurs in close to 100% of patients acutely, and about 70-90% patients in the delayed phase.[11,12] Aprepitant is, therefore, primarily used in the setting of CINV. The most important effect of neurokinin 1 (NK-1)-receptor antagonists is that they are able to markedly prevent both acute and delayed emesis induced by cisplatin and other chemotherapies in humans. It seems to have particular efficacy in the delayed phase, making it advantageous compared to other antiemetics, as they seem to be only efficacious in the acute phase.[12,13] According to guidelines of the American Society of Clinical Oncology, the dose for CINV is 125 mg prior to therapy, and then 80 mg on subsequent days.[14] It is given routinely in combination with 5-HT3 receptor antagonists and dexamethasone.[15]

Aprepitant and postoperative nausea and vomiting

Previous studies investigating the use of aprepitant for PONV have demonstrated results which are very promising. In a comparison prophylaxis study, ondansetron 4 mg IV and aprepitant 40 mg PO had similar effectiveness for the first 24 h. However, aprepitant was more effective in the subsequent 24-to 48-h postoperative time period,[16] with an effect on vomiting greater than on nausea.

For those undergoing abdominal surgery under different anesthetic techniques, aprepitant 40 mg or 125 mg was found to be more effective than ondansetron 4 mg IV in reducing nausea and vomiting in first 48 h period.[17] According to a study done by Lim *et al.*, the rate of occurrence of PONV assessed 6 h after surgery was lower for patients who were administered with ondansetron and 125 mg of aprepitant compared to the group that was only administered ondansetron.[18] There were also fewer patients who received rescue treatment in those who had received aprepitant 125 mg. The combination of aprepitant and ondansetron was found to significantly prolong the time to administration of the first rescue antiemetic drug compared with either drug alone, and almost completely prevented the occurrence of emesis.[19] Table 1 outlines various studies comparing aprepitant and other NK-1 inhibitors to ondansetron and/or placebo.[20]

The neurokinin 1 inhibitor drug group

In addition to aprepitant only, fosaprepitant and maropitant are in clinical use. Fosaprepitant is a water-soluable prodrug to aprepitant, used both in CINV and PONV. Maropitant is currently in use for motion sickness and vomiting in cats and dogs. According to a study done by Sedlacek *et al.*, maropitant was effective in preventing vomiting caused by stimulation of either central or peripheral emetic pathways whereas the other drugs examined prevented vomiting caused by central (metoclopramide and chlorpromazine) or peripheral (ondansetron) stimulation but not both.[21] Maropitant is still under investigation for use in humans. Other NK-1 receptor inhibitors include GR205171 (vofopitant, GlaxoSmithKline), CP-122721 (Pfizer), CJ-11974 (Pfizer), casopitant (GlaxoSmithKline), netupitant (Helsinn Healthcare), rolapitant or SCH 619734 (Schering-Plough), T 2328 (Mitsubishi Tanabe Pharma), and vestipitant (GlaxoSmithKline); however, they are still under investigation.[22]

Pharmacological properties

Substance P, a member of the tachykinin family of bioactive peptides, is a neurotransmitter in the afferent pathway of the emetic reflex.[23] The presence of substance P in regions of the brainstem involved in emesis in humans has been demonstrated.[24] The NK-1 receptor is the preferential site of action of the neuropeptide substance P in regions of the brainstem believed to mediate the emesis reflex.[25-27] Substance P is the natural ligand for the NK-1 receptor found to trigger its signaling and cause nausea and vomiting. NK-1 is widely expressed in the GI vagal afferents and brain areas involved in the vomiting reflex such as the nucleus solitary tract, [26-28] the area postrema of the CNS, as well as in the peripheral nervous system.[19]

Table 1: Summarized outcomes of neurokinin-1 inhibitors versus Zofran or placebo studies

Study	Ap (A) of Fos (F) or Cos (C) versus odansetron (Z) Ap (A) of Fos (F) or Cos (C) versus placebo (P)	Time (h)	Nausea	Vomiting	Rescue drug	Time to first vomit (h)	Complete response	Author conclusions
Habib, 2011	(A) 40 mg versus Z 4 mg	0-2 0-24 0-48	27/51 versus 27/53 (*P*=0.893) 33/51 versus 30/53 (*P*=0.398) 35/51 versus 32/53 (*P*=0.380)	3/51 versus 11/53 (*P*=0.026) 7/51 versus 19/53 (0.009) 8/51 versus 20/53 (*P*=0.011)	20/51 versus 24/51 (*P*=0.531) 31/51 versus 30/53 (*P*=0.665) 33/51 versus 32/53 (0.649)	44.4±11.7 versus 34.1±20 (*P*=0.008)	14/51 versus 21/53 (*P*=0.189) 11/51 versus 19/53 (*P*=0.132)	When combined with 10 mg dexamethasone, (A) 40 mg was more effective than (Z) 4 mg in preventing postoperative vomiting but not the incidence of nausea or need for rescue
Alonso-Damian, 2012	(A) 80 mg versus (Z) 4 mg	0-6 6-24 0-24	0/30 versus 10/30 (*P*=0.002) 0/30 versus 1/30 (*P*=0.313) 0/30 versus 1/30 (*P*=0.313)	0/30 versus 0/30 (*P*=1) 0/30 versus 1/30 (*P*=0.313) 0/30 versus 1/30 (*P*=0.313)	N/A	N/A	N/A	(A) 80 mg produced better control in preventing PONV in patients undergoing open cholecystectomy compared with (Z) 4 mg
Diemunsch, 2007	(A) 125 mg versus (A) 40 mg versus (Z) 4 mg	0-24 0-48	Peak nausea scores were lower in both (A) groups compared with (Z) groups	41/293 versus 47/293 versus 81/280 (*P*<0.001) 44/290 versus 53/292 versus 95/279 (*P*<0.001)	103/293 versus 97/293 versus 104/280 (*P*=0.599)	42.5±13.7 versus 41.3±15.1 versus 36.3±17.7 (*P*<0.001)	185/293 versus 188/293 versus 154/280 (*P*=0.049)	40 mg and 125 mg (A) were more effective than 4 mg (Z) for preventing vomiting at 24 and 48 h after open abdominal surgery
Gan, 2007	(A) 125 mg versus (A) 40 mg versus (Z) 4 mg	0-2 0-6 0-24	Peak nausea scores showed no difference among the groups	12/239 versus 25/248 versus 63/246 (*P*<0.001) 16/239 versus 36/248 versus 80/246 (*P*<0.001)	134/239 versus 136/248 versus 133/246 (*P*=0.905)	45.7±9.3 versus 43.4±12.2 versus 36.3 +17.8 (*P*<0.001)	103/239 versus 112/248 versus 103/246 (*P*=0.757)	40 mg and 125 mg of (A) were superior to 4 mg of (Z) for preventing vomiting in first 24 and 48 h, but not nausea control, the use of rescue drug or complete response
Jung, 2013	(A) 80 mg versus (A) 125 mg versus P	0-2 2-24 24-48	14/40 versus 14/40 versus 25/40 (*P*<0.05) 11/40 versus 8/40 versus 16/40 2/40 versus 3/40 versus 1/40	0/40 versus 0/40 versus 3/40 0/40 versus 0/40 versus 8/40 (*P*<0.05) 0/40 versus 0/40 versus 0/40	3/40 versus 4/40 versus 8/40	N/A	N/A	A 80 and 125 mg orally seemed to be promising as prophylactic antiemetics in patients with high susceptibility for PONV when administering opioid based IV PCA. No statistical significant difference in reduction in delayed PONV in 2-48 h except (A) 125 mg, 2-24 h postoperative
Tsutsumi, 2014	(F) 150 mg versus (O) 4 mg	0-2 0-24 0-48	8/32 versus 12/32 11/32 versus 18/32 12/32 versus 18/32	2/32 versus 8/32 2/32 versus 16/32 (*P*<0.001) 2/32 versus 16/32 (*P*<0.05)	6/32 versus 8/32 8/32 versus 14/32 10/32 versus 14/32	Patients in the F group had a longer time to vomiting than O group (*P*<0.001)	23/32 versus 20/32 1/32 versus 13/32 (*P*=0.045) 20/32 versus 12/32	(F) significantly prevented vomiting in the first 24 and 48 h after craniotomy compared to (O). However, (F) was not more effective in preventing nausea than (O)
Altorjay, 2011	(C) 50 mg versus P	0-24 24-48 0-48	20/233 versus 38/235 (*P*=0.013)	24/233 versus 59/235 (*P*<0.001)	60/233 versus 73/235 (*P*=0.203) 14/233 versus 14/235 (*P*=0.981)	44.0±12.1 versus 38.8±16.8 (*P*<0.05)	160/233 versus 138/235 (*P*=0.025) 163/233 versus 149/235 (*P*=0.133)	The combination of (C) 50 mg and (Z) 4 mg, superior only in preventing postoperative emesis

AP = Aprepitant, Fos = Fosaprepitant, Cos = Casopitant N/A = Not available, PONV = Postoperative nausea and vomiting, PCA = Patient-controlled analgesia

Aprepitant is a NK-1 receptor antagonist which is highly selective and centrally acting, with a half-life of 9-12 h.[28,29] It has a bioavailability of 65%.[30] Aprepitant has the chemical name 5-([[2R, 3S]-2-[[1R]-1-[3,5-bis [trifluoromethyl] phenyl] ethoxy]-3-[4-fluorophenyl]-4 morpholinyl]methyl)-1,2-dihydro-3H-1,2,4-triazol-3-one.

Aprepitant undergoes oxidation at the morpholine ring and its side chains, and it is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. It is also found to be a weak inhibitor of CYP2C19 and CYP2C9, a moderate inhibitor of CYP3A4 and an inducer of CYP2C9; therefore, there is potential for drug interactions.[30] Aprepitant is eliminated mainly by excretion of metabolites in feces and urine.[31]

Aprepitant dosing, side effects, and cost

Aprepitant, which is made in capsular form, is administered orally, 1-2 h preoperatively, for PONV prophylaxis.[2] A typical dose is 40 mg, although doses up to 125 mg for PONV have been studied. Fosaprepitant, a pro-drug is available for intravenous administration, with a typical dose of 115 mg.[30] Fosaprepitant, is only Food and Drug Administration approved for use in CINV although it has been shown to more effective than ondansetron in reducing vomiting in gynecologic, neurological, and lower limb surgeries.[32-34] Aprepitant is relatively safe; however, common side effects include dizziness, constipation, and hypotension, especially when used in the setting of PONV prophylaxis. In the setting of CINV prophylaxis, common side effects are fatigue, diarrhea, weakness, indigestion, abdominal pain, hiccups, leukopenia, dehydration and altered liver function tests, cough, and hiccups.[35]

The cost of a 80 mg capsule is approximately US$100 and a 125 mg capsule is about US$110.[36] There is no generic form available; so it is considerably costly compared to other antiemetics, such as ondansetron, which became generic in 2007.[31]

Conclusion

Aprepitant, a NK 1 receptor antagonist, exerts its effects via a common pathway of the emetic centers after crossing the blood brain barrier. Aprepitant is a drug with limited side effect profile and works very efficiently for PONV. Dosed alone or in combination with other antiemetics, this medication has shown tremendous relief of symptoms and for a prolonged period of time. The novel drug has addressed both acute and delayed onset of nausea and vomiting, which is very useful in the postoperative population because it decreases the need for rescue doses later in the postoperative period. It should be noted that aprepitant has been found to be more effective than ondansetron at preventing PONV in the perioperative period.[37]

The major drawback and limitation of aprepitant for its use is that it is expensive, making it difficult to justify its use outside of very severe symptoms or potential risk factors for nausea and vomiting. Hopefully, prices will become more competitive in the future and allow for the integration of this effective medication for everyday use of prophylaxis for PONV.

All classes of antiemetics, including aprepitant, have demonstrated efficacy for the treatment of nausea and vomiting. However, much of the data is contradictory given the complex multifactorial nature of PONV, and thus, no one agent is likely to prevent PONV in all patients. Ongoing and future large studies are warranted to best sort out the role for aprepitant vis-à-vis individual variables and best practice strategies in high-risk patients, which ultimately increase patient comfort, satisfaction, and minimize morbidity associated with extended PACU times and unplanned hospital stays.

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Conflicts of interest

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